Mucosal healing is not associated with better outcome during seven years of follow-up in pediatric patients with Crohn's disease

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Abstract

Background

Mucosal healing (MH) has become a perspective treatment target in patients with Crohn's disease (CD). Data about the impact of MH on long-term outcome in pediatric patients are still scarce.

Methods

76 pediatric patients with CD were evaluated retrospectively (2000–2015) in a tertiary care center. Based on MH achievement, they were divided into two groups (MH, n = 17 and No MH, n = 59). The primary endpoint was to assess the association of MH and the need for CD-related hospitalizations or surgery in pediatric patients with CD.

Results

The number of hospitalized patients was 24% in the MH group and 42% in the No MH group, P = 0.26. The total number of CD-related hospitalizations was not significant between the MH group and the No MH group (5 vs. 41, P = 0.15). The time to the first hospitalization was 24 months in MH and 21 months in No MH, p > 0.99. 24% patients in the MH group and 39% patients in the No MH group underwent CD-related operation, P = 0.39. Time to the first operation was 43 months for MH and 19 months for the No MH group, P = 0.13. The follow-up period was 91 months in the MH group and 80 months in the No MH group, P = 0.74. The use of infliximab was positively associated with MH, P = 0.002.

Conclusions

MH was not associated with fewer CD-related hospitalizations or operations in pediatric patients with CD during seven years of follow-up.

Background

It seems to be promising to accomplish mucosal healing (MH) in patients with Crohn's disease (CD). However, the absence of a unique MH definition can make the comparing of data from clinical trials more challenging. It is known that treatment based only on the disappearance of the symptoms is inadequate for the proper monitoring of the disease activity (1). It has been shown in adult patients with CD that MH is associated with a lower risk of surgical resection, lower hospitalization rate, decreased risk of relapse, and prolonged steroid-free remission (2–5). However, some recent pediatric data indicate no benefit of MH on CD-related hospitalizations and surgery (6). More extensive pediatric data about MH and long-term outcome are still sparse. MH achieved with exclusive enteral nutrition (EEN) in children showed potential benefit for the relapse rate in comparison with corticosteroid (CS) treatment during a one-year

follow-up (7). Complete endoscopic healing in children correlated with a decreased clinical relapse rate and lower intestinal resection during three years of follow-up (8). Our study aimed to assess the long-term outcome in pediatric patients with CD according to MH.

Methods

Design

The primary goal was to assess the rate and time interval of CD-related hospitalizations and operations after the follow-up (2nd) colonoscopy. The first colonoscopy was performed during the initial diagnostic workup at the time of diagnosis. Furthermore, the Pediatric CD Activity Index (PCDAI) was recorded. The second colonoscopy was indicated after the introduction of therapy within week 16 up to week 38 of new treatment according to clinical symptomatology. At the time of the 2nd colonoscopy, MH was assessed (with histology), and laboratory parameters of inflammation (C-reactive protein and erythrocyte sedimentation rate (ESR)) were recorded. According to MH achievement, the patients were divided into two groups: “MH” and “No MH.”

Patients

Pediatric patients with CD from a single tertiary care center of the University Hospital in Hradec Králové were evaluated retrospectively (2000–2015) and followed till January 2019. CD diagnosis was made according to the Porto criteria (9). The phenotype of the CD was estimated by the pediatric modification of the Montreal classification (10). The upper gastrointestinal tract was examined by esophagogastroduodenoscopy, while magnetic resonance enterography was used to examine the small bowel. Inflammatory bowel disease in a first-degree relative was marked (Table 1). Perianal disease included anal fissure. PCDAI was used for the evaluation of the clinical and laboratory activity of the disease (11). The study follows the principles outlined in the Declaration of Helsinki. Informed consent was not obtained from the patients or parents because of the retrospective character of the study.

Table 1
Study group characteristics.

	MH **n = 17**	**No MH** **n = 59**	**P value**
Ethnicity	17 Caucasian	59 Caucasian	
Gender (M/F), %	11/6 65%/35%	31/28 53%/47%	0.42
Age of diagnosis (years), [median, IQR]	11.5 [10.9–15.9]	14.0 [12.1–15.4]	0.33
Weight at diagnosis (kg), [median, IQR]	37.0 [30.3–53.0]	40.0 [31.0-51.5]	0.89
Weight at 2nd colonoscopy (kg) [median, IQR]	60.0 [46.0–70.0]	53.0 [44.0–60.0]	0.09
Family history (positive/negative)	3/14	7/52	0.68
Paris classification, n (%)			
Location			
L1	2 (12%)	21 (36%)	0.08
L2	2 (12%)	5 (8%)	0.65
L3	13 (76%)	33 (56%)	0.16
L4a (positive/examined)	3/7 (41%)	6/15 (25%)	1.0
L4b (positive/examined)	5/17 (29%)	11/55 (20%)	0.51
Behavior			
B1	15 (88%)	54 (92%)	0.65
B2	2 (12%)	3 (5%)	0.31
B3	0 (0%)	2 (3%)	1.0

Bold font indicates P value < 0.05.

L1 – distal 1/3 ileum ± limited cecal disease; L2 – colonic disease; L3 – ileocolonic, L4a – upper disease proximal to ligament of Treitz; L4b - upper disease distal to ligament of Treitz and proximal to distal 1/3 ileum. B1 – non-stricturing and non-penetrating, B2 – stricturing, B3 – penetrating

Abbreviations: ASCA, anti-Saccharomyces cerevisiae antibodies, CRP, C-reactive protein, ESR, erythrocyte sedimentation rate; IQR, interquartile range; MH, mucosal healing, PCDAI, Pediatric Crohn´s Disease Activity Index.

	MH n = 17	No MH n = 59	P value
p (perianal disease - including anal fissure)	5 (29%)	9 (15%)	0.28
Period (1st -2nd colonoscopy) (months), [median, IQR]	28 [17–36]	21 [13–38]	0.31
Period of observation (months), [median, IQR]	91 [51–113]	80 [48–105]	0.74
PCDAI (1st colonoscopy), [median, IQR]	27.5 [21.3–38.8]	25.0 [17.5–32.5]	**0.01**
ASCA IgA at diagnosis (U/ml) [median, IQR], examined, n (%)	280.0 [11.5–300.0] 9 (53%)	225.5 [36.3–300.0] 32 (54%)	0.69
ASCA IgG at diagnosis (U/ml) [median, IQR], examined, n (%)	39.0 [5.0-102.0] 7 (41%)	74.0 [43.7-157.5] 29 (49%)	0.06
ESR (1st /2nd hour) (2nd colonoscopy) [median, IQR], examined, n (%)	7 / 19 [4.0-14.3] [10.8–32.5] 14 (82%)	24 / 48 [12.0–35.0] [28.0–70.0] 51 (86%)	**0.0003** **0.0001**
CRP, mg/l (2nd colonoscopy), [median, IQR]	0.3 [0.05-2.0]	8.4 [4.0-17.4]	**< 0.0001**
Bold font indicates P value < 0.05.			
L1 – distal 1/3 ileum ± limited cecal disease; L2 – colonic disease; L3 – ileocolonic, L4a – upper disease proximal to ligament of Treitz; L4b - upper disease distal to ligament of Treitz and proximal to distal 1/3 ileum. B1 – non-stricturing and non-penetrating, B2 – stricturing, B3 – penetrating			
Abbreviations: ASCA, anti-Saccharomyces cerevisiae antibodies, CRP, C-reactive protein, ESR, erythrocyte sedimentation rate; IQR, interquartile range; MH, mucosal healing, PCDAI, Pediatric Crohn´s Disease Activity Index.			

MH definition

We defined MH as a combination of total endoscopic and histological healing. MH was determined as complete endoscopic disappearance of all mucosal ulcerations (including aphthous ulcers) and the absence of any signs of mucosal inflammation (erythema, edema) in the terminal ileum and large bowel. A complete colonoscopy with terminal ileum intubation was performed on all MH patients. In 6 of the No MH patients, the terminal ileum was not intubated, and in 11 patients, a histology sample was not obtained. In all of these patients, endoscopic findings showed apparent signs of inflammation. In most patients (and all MH patients), at least one histologic sample from the terminal ileum and one from the colon were taken. In the normal-appearing bowel segments, the biopsies were taken randomly. Biopsy specimens were stained with hematoxylin and eosin and read by experienced pathologists. Histologically, we distinguished low, medium, and high inflammatory activity based on the description by the pathologists. In the case of a normal endoscopic assessment but with histological signs of high inflammatory activity, the patient was classified as “No MH.”

Operations and hospitalizations

CD-related surgical interventions were represented mainly by major abdominal surgery, then anal fistula surgery, and anal divulsion. In some patients, a combined surgical procedure was performed. CD-related hospitalizations included only admissions for deterioration in disease activity. Hospitalizations for operation were assessed separately. Repetitive surgical procedures and hospitalizations were recorded during the whole follow-up period.

Therapy

Any therapy between the 1st and 2nd colonoscopy and immediately after the 2nd colonoscopy was registered. EEN given for at least four weeks was recorded. Treatment with 5-aminosalicylic acid (5-ASA), adalimumab (ADA), azathioprine (AZA), CS, infliximab (IFX), methotrexate (MTX), or mycophenolate mofetil was documented.

Statistical methods

For the patients’ characteristics, descriptive analysis (median and interquartile ranges [IQR]) was used. Normality was tested with the D’Agostino-Pearson omnibus normality test. t-test and, for dichotomous data, Fisher’s exact test were performed for the comparison of variables between the two groups. For variables without normal distribution, we used Mann-Whitney U-test. Differences were considered statistically significant at a value of $p < 0.05$. The calculations (except for the statistical power) were carried out using GraphPad Prism 6 (GraphPad Software, Inc.). For the time-to-event survival analysis, Kaplan Meier curves were constructed. There were no missing data during the follow-up.

Results

Baseline characteristics

From 146 pediatric patients with CD, we excluded patients with missing data (n = 42), patients who had undergone an operation for CD before the 2nd colonoscopy (n = 24), patients who appeared to be non-compliant (n = 4), and those with confirmed infectious gastroenteritis at the time of colonoscopy (n = 1). 76 patients (age 4.1–17.8 years) were finally enrolled. There was no difference in gender, age, weight, disease location or phenotype between the MH and No MH groups (Table 1). Initially, a higher CD activity was observed in patients who later attained the MH group (PCDAI 27.5 [21.3–38.8] vs. 25.0 [17.5–32.5], P = 0.01 (Table 1). At the time of the 2nd colonoscopy, the laboratory activity of the CD was significantly lower in the MH group in comparison with the No MH group (CRP 0.3 mg/l [0.05-2.0] vs. 8.4 mg/l [4.0-17.4]), $p < 0.0001$, ESR 7/19 vs. 24/48, P = 0.0003 and P = 0.0001). The interval between the 1st and 2nd colonoscopy did not differ statistically between the MH and No MH groups (28 months [17–36], vs. 21 [13–38], P = 0.31) (Table 1). The observational period after the 2nd colonoscopy was 91 months [51–113] vs 80 months [48–105], P = 0.74 for the MH vs. No MH group (Table 1).

Hospitalizations

The number of patients who required CD-related hospitalization was 24% in the MH group and 42% in the No MH group, P = 0.26. The total number of hospitalizations in the MH and No MH groups did not differ significantly (5 vs. 41, P = 0.15) (Table 2). The time to the first hospitalization was also similar for the MH group (24 months [8–27]) and the No MH group (21 months [6–35]), $p > 0.99$ (Table 2), also shown in the survival data curve (Fig. 1).

Table 2
CD-related hospitalizations and operations in MH and No MH groups.

	MH **n = 17**	**No MH** **n = 59**	**P value**
Hospitalization (Power 25.1%)	4 (24%)	25 (42%)	0.26
Time to hospitalization (months), [median, IQR]	n = 4 24 [8–27]	n = 25 21 [6–35]	> 0.99
Total number of hospitalizations	5	41	0.15
Major + perianal operation	4 (24%)	23 (39%)	0.39
Major operation (Power 44.4%)	3 (18%)	23 (39%)	0.15
Time to operation (months), [median, IQR]	n = 4 43 [19–69]	n = 23 19 [1.0–45]	0.13
Total number of operations	6	33	0.31
Bold font indicates P value < 0.05.			
Abbreviations: IQR, interquartile range; MH, mucosal healing.			

Operations

Four patients (24%) from the MH group underwent CD-related surgery, which was not significantly different from the No MH group (23 patients, 39%) P = 0.39 (Table 2), as shown in the survival curve (Fig. 2). In total, there were six operations (in 4 patients) in the MH group and 33 operations in 23 patients from the other group, P = 0.37 (Table 2). In some of the patients, the procedures were combined (Additional file 3: Table S3). All operated patients from the No MH group underwent a major operation. One patient from the MH group had only a perianal operation. The time to the first operation did not achieve statistical significance between the groups (MH 43 months [19–69] and No MH 19 months [1.0–45], P = 0.13) (Table 2).

Therapy

Between the 1st and 2nd colonoscopy, 9 (53%) patients in the MH group were treated with IFX in comparison with 8 (14%) in the No MH group, P = 0.002 (Additional file 1: Table S1). There was no statistical difference between the groups for any of the other therapies. In 10 (59%) patients, therapy with AZA or IFX was interrupted immediately after achievement of MH assessed by the 2nd colonoscopy. However, in most patients N = 4 (80%) initially treated with both IFX and AZA, either of the drugs was continued after the 2nd colonoscopy. IFX or adalimumab was introduced to 12 (20%) patients in the No MH group (Additional file 2: Table S2). Unhealed patients who were introduced to anti-TNF therapy did not require less CD-related hospitalization (P = 0.21) or operation (P = 0.33) than patients with no anti-TNF therapy (Table 3).

Table 3
CD-related hospitalizations and operations in No MH group. Introduction of anti-TNF therapy after 2nd colonoscopy.

	Anti-TNF YES n = 12	**Anti-TNF NO n = 47**	**P value**
Hospitalization (Power 37.5%)	3 (25%)	22 (52%)	0.21
Time to hospitalization (months), [median, IQR]	n = 3 22 [2–40]	n = 22 20 [6–34]	0.97
Total number of hospitalizations	5	36	0.26
Major + perianal operation	3 (25%)	20 (43%)	0.33
Major operation	3 (25%)	20 (43%)	0.33
Time to operation (months), [median, IQR]	n = 3 39 [9–45]	n = 20 17 [1–31]	0.30
Total number of operations	3	30	0.22
Bold font indicates P value < 0.05.			
Abbreviations: IQR, interquartile range; MH, mucosal healing.			

Discussion

In our study of pediatric patients with CD, we proved that MH at the time of the first follow-up endoscopy is not associated with a more favorable outcome in the number of CD-related hospitalizations or operations during the next seven years of observation. In adult patients, a lower hospitalization rate was

observed during eight years (96 months) of follow-up (3). An endoscopic substudy of a Step-up/Top-down trial on 49 pediatric patients did not find a difference in the time to the first CD-related hospitalization (P = 0.67) (6), which is in line with our results. It has been shown in adult patients with CD that MH is linked to a lower risk of surgical resection (3). We observed that 24% patients from the MH group and 39% from No MH group required a CD-related surgery during 7.5 resp. 6.6 years of observation, which was not significantly different. The time to the operation was also not statistically significantly different between the groups. This finding is consistent with data from the previously mentioned pediatric study from Hoekman et al. (6) (P = 0.5). We propose two possible explanations for the similarity of the results in the number of operated as well as hospitalized patients in our cohort. First, 59% of the patients in the MH group were weaned from AZA or IFX immediately after the 2nd colonoscopy after MH attainment, whereas in 80% of patients initially treated with both IFX and AZA, one of the drugs was continued after MH achievement. Furthermore, the effect of withdrawal of either AZA or IFX in patients with quiescent CD is still uncertain (12). This decision could also be justifiable, especially in children, due to the possible adverse effects of combination therapy (13–15). Importantly, in 20% of patients from the No MH group, IFX or adalimumab was introduced after endoscopic proof of activity. In total, in 47% of patients, some treatment was launched (5-ASA, ADA, AZA, CS, EEN, IFX, mycophenolate mofetil) which could have had a positive influence on the disease course and consequent prognosis. However, we did not prove that the launch of anti-TNF alone would have had a positive effect on hospitalizations or operations in unhealed patients. Paradoxically, we observed initially higher CD activity in patients who later attained MH (Table 1). Maybe the more aggressive therapy at the beginning can add to the higher rate of MH, as has been demonstrated in adults (16). There was greater use of IFX between the 1st and 2nd colonoscopy in the group that later reached MH. The premise that IFX is a potent drug in the induction of MH in patients with CD has been proven in children as well as in adults (17, 18). Still debatable is a widely-adopted definition of MH. Because of the retrospective character of the study, we did not use either of the indexes for the assessment of MH (SES – CD, Simple Endoscopic Score for Crohn's Disease, or CDEIS, Crohn's disease endoscopic index of severity). Nevertheless, MH, as defined by us, corresponded with SES-CD = 0. This definition is used frequently (5, 19). We are aware of other limitations of our research. The 2nd colonoscopy was not scheduled, and so the time interval between colonoscopies is vast. The indication for the 2nd colonoscopy was not always traceable, and hence it was not possible to subcategorize the patients according to this. Some patients required colonoscopy because of clinical symptoms. In some patients drug reduction was intended in case of the favorable finding. In others, it was part of a scheduled checkup. Furthermore, the number of patients allocated to the MH group was quite low. At the time of MH assessment, we did not search for MH in the whole GIT tract but only in the colon and terminal ileum. We also would have appreciated having the values from the fecal calprotectin test. Finally, the approach to therapy has changed during the 16 years (2000–2015).

In conclusion, the use of IFX was associated with an increased probability of MH achievement in our group. We showed that patients with MH do not undergo fewer CD-related hospitalizations or operations, and there are indications that even later optimization of the therapy can still lead to a good clinical

outcome. On the other hand, these results can also indicate the necessity for prolonged treatment, despite MH having been achieved.

Abbreviations

5-ASA, 5-aminosalicylic acid; ASCA, anti-Saccharomyces cerevisiae antibodies; AZA, azathioprine; CD, Crohn's disease; CDEIS, Crohn's disease endoscopic index of severity; CS, corticosteroids; EEN, exclusive enteral nutrition; ESR, erythrocyte sedimentation rate; IFX, infliximab; MH, mucosal healing; MTX, methotrexate; PCDAI, Pediatric Crohn's Disease Activity Index; SES CD, Simple Endoscopic Score for Crohn's Disease

Declarations

Ethics approval and consent to participate:

The study follows the principles outlined in the Declaration of Helsinki. Informed consent was not obtained from the patients and parents because of the retrospective character of the study.

Consent for publication:

Not applicable.

Availability of data and materials:

The dataset is available from the corresponding author on request.

Competing interests:

The authors declare that they have no competing interests.

Authors'contributions

JM, MŠ, OP, JB designed the study. JM, PD, RŠ, JK, LD, TV collected the data. JM, TD, IT, analyzed the data and interpreted the results. JM, MŠ, RŠ, JK and LD drafted the manuscript. TV, JB, PD, TD revised the manuscript. JM, MŠ, PD, IT, TV and JB interpreted the data and reviewed the manuscript. All authors read and approved the final manuscript.

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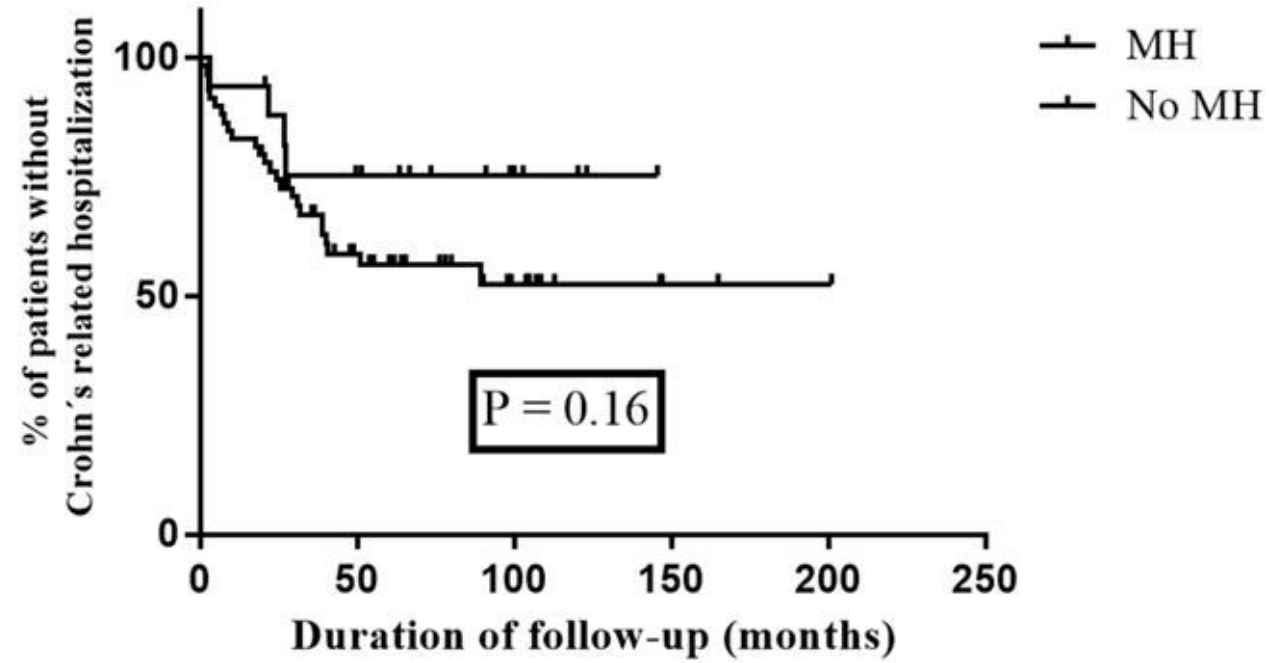
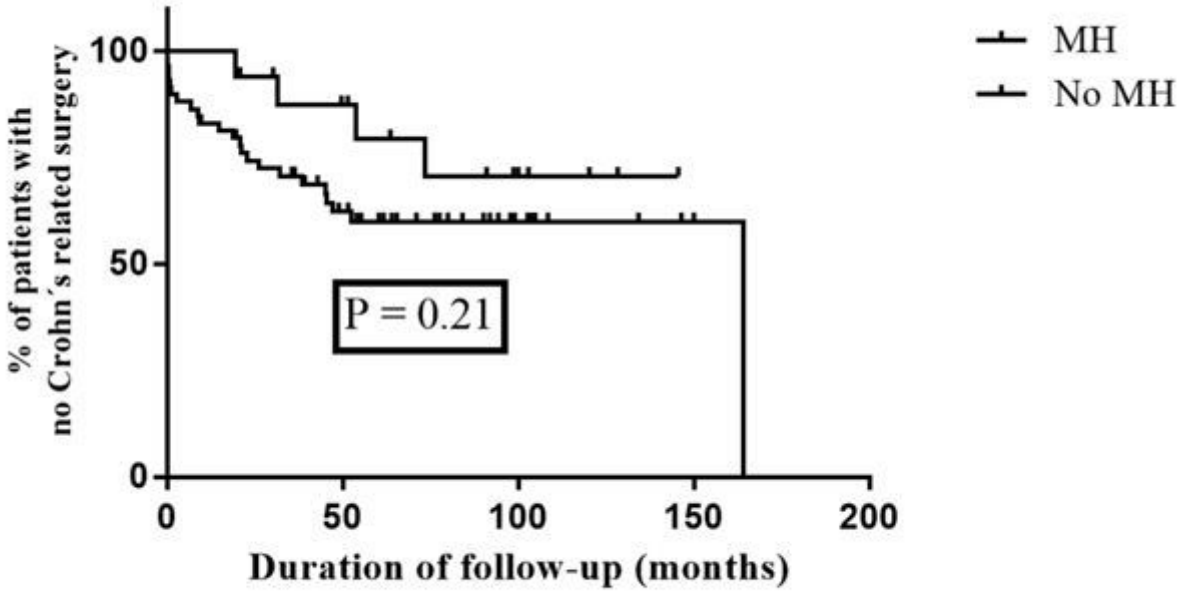
Figures



Abbreviations: MH, mucosal healing.

Figure 1

Survival curve. CD-related hospitalizations between MH and No MH groups



Abbreviations: MH, mucosal healing.

Figure 2

Survival curve. CD-related operations between MH and No MH groups

Supplementary Files

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